II. REMARKS

Formal Matters

Claims 1-26 and 28-64 are pending after entry of the amendments set forth herein.

Claims 1-8, 16, 20, 27, and 33 were examined and were rejected. Claims 9-15, 17-19, 21-26, 28-32, and 34-62 were withdrawn from consideration.

Claims 1, 20, and 33 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 20, and 33 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 12, lines 20-25; and Example 3. Accordingly, no new matter is added by these amendments.

Please replace claims 1, 20, and 33 with the clean version provided above.

Claim 27 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 63 and 64 are added. Support for new claims 63 and 64 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary location: Example 3. Accordingly, no new matter is added.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Information Disclosure Statement

Applicants file herewith an Information Disclosure Statement, which provides:

1) a copy of Reid et al., "Radial Migration of Subependymal Cells in the Adult Rodent Forebrain", *Society of Neuroscience* – ABSTRACTS, Vol. 22 Part 3, 26th Annual Meeting, Washington, D.C. November 16-21 1996 ("Reid, 1996 Abstract"); and

2) a copy of James Steven Reid's doctoral thesis ("Reid thesis").

1) Reid 1996 Abstract

As explained in the amendment, filed on September 16, 2002 and responsive to the May 6, 2002 Office Action in parent case U.S. Serial No. 09/129,028, the Reid 1996 Abstract is not available as prior art under 35 U.S.C.§102 against the present application.

Applicants' disclosure of their own work within one year before the application filing date cannot be used against them under 35 U.S.C.§102(a). Therefore, where the applicants are co-authors of a publication cited against their application, the publication may be removed as a reference by submission of a declaration establishing that the article is describing applicants' own work, *i.e.*, that the publication is not "by another." The courts have found that persons involved only with assay and testing are normally listed as coauthors but are not considered co-inventors.[1] Authorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article. Thus, co-authors may not be presumed to be coinventors merely from the fact of co-authorship.

The situation in the present application is similar to that of *In re Katz*. First, the September 17, 1996 date is less than one year before the August 4, 1997 priority date of the instant application. Second, the authors listed on the Reid Abstract are Reid, Patel, and Fallon. Patel is not a co-inventor of the present application. Patel is not an inventor, as he was working under the direction of Fallon, and did not contribute to the inventive concept. Accordingly, the Reid 1996 Abstract is the inventors' own work, and as such is not invention "by another." A copy of the Declaration under 37 C.F.R.§1.132 by

[1] In *In re Katz*, 215 USPQ 14 (CCPA 1982), Katz stated in a declaration that the coauthors of the cited publication, Chiorazzi and Eshhar, "were students working under the direction and supervision of the inventor, Dr. David H. Katz." The court held that this declaration, in combination with the fact that the publication was a research paper, was enough to establish Katz as the sole inventor and that the work described in the publication was his own. In research papers, students involved only with assay and testing are normally listed as coauthors but are not considered co-inventors.

Dr. James Fallon, which was made of record in the 09/129,028 application, attests to this fact and is provided herewith as Exhibit 1.

Therefore, in view of the evidence in the form of the Declaration of James Fallon under 37 C.F.R.§1.132, the Reid 1996 Abstract is not available as prior art under 35 U.S.C.§102 against the present application, as it is derived from the inventors' own work.

2) Reid thesis

A copy of the doctoral thesis of inventor James Steven Reid is provided herewith. The Reid thesis is not available as prior art to the instant application under 35 U.S.C.§102.

As discussed in MPEP §2128.01, a doctoral thesis is available as prior art as a "printed publication" only when indexed, cataloged, and shelved in a library such that it is sufficiently accessible to the public. The Reid thesis was deposited with the Office of Graduate Studies at the University of California, Irvine, in March, 1997. However, the Reid thesis was not cataloged in the University library until October 15, 1997. Thus, the Reid thesis was not available to the public as a printed publication until after the August 4, 1997 priority date of the instant application. Accordingly, the Reid thesis is not available as prior art to the instant application under 35 U.S.C.§102.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-8, 20, 27, and 33 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description. Claims 1-8, 20, 27, and 33 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

Written description

The Office Action stated that while the disclosure teaches that TGF-α is a molecule that binds EGF receptor (EGF-R), the recitation of ill described molecules which maintain such functional activities merely represents a functional recitation of multiple distinct classes of molecules that are not structurally described but which are encompassed by the claims. Applicants respectfully traverse the rejection.

All that is necessary to fulfill the written description requirement is that one of skill in the art recognize that the Applicants invented what is claimed. MPEP §2163.02. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow

persons of ordinary skill in the art to recognize that he or she invented what is claimed." Applicants submit that those skilled in the art would recognize that Applicants invented what is claimed.

The instant specification provides an ample description of compounds that were known in the art to bind and activate an EGF-R, including EGF, TGF-α, betacellulin, heparin binding EGF-like factor, amphiregulin, heregulin, and neuregulin-3, and variants thereof. Specification, e.g., page 12, line 28 to page 13, line 6. The Office Action stated that while the disclosure teaches that TGF-α is a molecule that binds the EGF-R, "the recitation of alterative ill described molecules which maintain such functional activities as noted above merely represents a functional recitation of multiple distinct classes of molecules which are not structurally described but which are encompassed by the claims." Office Action, page 3. However, many of the compounds discussed in the specification were well known in the art at the time of filing. It was further known that a number of EGF-R ligands share structural features. These structural features are depicted in the amino acid sequence alignment, provided herewith as Exhibit 2.

The instant specification provides working examples of the use of TGF-α to attract a glial progenitor cell to a site of CNS lesion or damage. Specification, e.g., Example 3. Based on Applicants' disclosure, those skilled in the art would reasonably expect that other EGF-R binding compounds would also function to attract a glial progenitor cell to a site of CNS lesion or damage.

Enablement

The Office Action stated that the specification is enabling for TGF-α binding to the EGF receptor, and stated that the specification does not reasonably provide enablement for the generic recitation of all compounds that bind to the EGF receptor to attract a glial progenitor cell or progeny thereof or to stimulate differentiation as claimed. Applicants respectfully traverse the rejection.

The enablement requirement of 35 U.S.C.§112, first paragraph, requires that an Applicant teach how to make and use the invention commensurate in scope with the claims. Applicants have shown by working example that an EGF-R binding ligand, when administered outside the ventricles to an animal having CNS damage or lesion, is effective in attracting a glial progenitor cell or its progeny to the site of CNS damage or lesion. Applicants have also provided abundant description of how to determine whether a given EGF-R binding compound attracts a glial progenitor cell or its progeny to the site of CNS damage or lesion. Applicants submit that the enablement requirement of 35 U.S.C.§112, first

paragraph, has been met.

The instant specification provides ample description of methods for attracting a glial progenitor cell or progeny thereof to a site of CNS lesion or damage. Specification, e.g., page 12, lines 3-8; and Example 3 (beginning on page 68). The specification provides **working examples** of methods for attracting a glial progenitor cell or progeny thereof to a site of CNS lesion or damage in a mammal, comprising administering a compound that binds an EGF-R to the mammal. The working example exemplifies use of TGF-α.

The specification further provides ample description, including by working example, of how to determine whether a given compound binds an EGF-R, and how to determine whether a given compound that binds an EGF-R attracts a glial progenitor cell or progeny thereof to a site of CNS lesion or damage. Specification, page 29, lines 7-24; and Example 3, page 68 et seq.

Applicants are not required under 35 U.S.C.§112, first paragraph, to show that each and every compound that binds an EGF-R will function in the methods as claimed. Furthermore, the claims require that a glial progenitor cell or its progeny be attracted to a site of CNS damage or lesion. Thus, the claims exclude compounds that, when administered as claimed, do not attract a glial progenitor cell or its progeny to a site of CNS damage or lesion.

In view of the description in the specification, including working examples, of methods for attracting a glial progenitor cell or progeny thereof to a site of CNS lesion or damage, those skilled in the art would reasonably expect that other compounds that bind EGF-R would also attract a glial progenitor cell or progeny thereof to a site of CNS lesion or damage.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-8, 20, 27, and 33 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claim 20 was rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that claims 20 is incomplete for omitting essential steps, the omitted steps being those steps which link the in vitro administration of the compound to the method as claimed in claim 1.

The Office Action suggested the recitation "wherein the CNS tissue is in tissue culture." Applicants thank the Office for the helpful suggestion, which is incorporated into claim 20.

Applicants submit that the rejection of claim 20 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(a)

Claims 1-7, 16, and 33 were rejected under 35 U.S.C.§102(a) as allegedly anticipated by Reid et al. ("Radial Migration of Subependymal Cells in the Adult Rodent Forebrain" Abstract, 8-7-97; hereinafter "the Reid Abstract").

The Office Action stated that the Reid Abstract teaches striatal infusion of TGF-α in lesioned dopaminergic nigrostriatal pathway, and that the infused TGF-α induces cells in the subependymal zone to proliferate and migrate radially into the overlying striatum. The Office Action concluded that the Reid Abstract anticipates the claimed invention. Applicants respectfully traverse the rejection.

The Reid Abstract is not available as prior art under 35 U.S.C.§102(a). The Reid Abstract was published on August 8, 1997. The instant application claims benefit of the August 4, 1997 filing date of U.S. Provisional Application No. 60/055,383. Hence, the effective filing date of the instant application is August 4, 1997. Since the Reid Abstract published after the effective filing date of the instant application, the Reid Abstract is not available as prior art under 35 U.S.C.§102(a).

Applicants submit that the rejection of claims 1-7, 16, and 33 under 35 U.S.C. §102(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(e)

Claims 1-8, 16, and 33 were rejected under 35 U.S.C.§102(e) as allegedly anticipated by Weiss et al. (U.S. Patent No. 5,980,885; "Weiss").

The Office Action stated that Weiss teaches administration of TGF-α to brain for the purpose of inducing in vivo proliferation, migration and differentiation of neural and/or glial cells and for treatment of Huntington's, Alzheimer's, Parkinson's and other neurological disorders. The Office Action stated that as the treatment of Weiss involves administration of TGF-α to the brain and results in the contact of TGF-α, a compound that binds the EGF receptor with neural progenitor cells within the brain, the treatment taught by Weiss is necessarily the same as that claimed because the treatment comprises the same reagents, steps, and effects. Applicants respectfully traverse the rejection.

Without conceding as to the correctness of the rejection, claim 33 is amended to recite "to a site of CNS damage or lesion," and "wherein the administration is outside the ventricles."

Weiss only discusses administration to the ventricles.

Weiss does not disclose a treatment method that comprises the same reagents, steps, and effects as the instant claims. Weiss only shows **intraventricular** injection of growth factors to animals that have no CNS damage or lesion. Weiss, Examples 27-30. Weiss states that EGF was infused into the lateral ventricles (Weiss, Example 27, column 47, lines 12-16); that EGF and FGF were administered into the ventricular system (Weiss, Example 28, column 47, lines 59-63); that EGF or FGF or EGF and FGF together were administered into the lateral ventricle (Weiss, Example 29, column 48, lines 8-11); and that EGF was administered into the fourth ventricle (Weiss, Example 30, column 48, lines 27-32).

Weiss states repeatedly that growth factors are delivered to the **ventricles**. Weiss, column 17, lines 8-19; column 26, lines 3-10; and column 26, lines 16-20. However, administration of TGFα, or functional fragments thereof, to the ventricles does not function to induce migration of a glial progenitor cell toward a site of CNS damage or lesion.

Weiss states:

> "The number of neural stem cell progeny **proliferated** in vitro from th mammalian CNS can be increased dramatically by injecting a growth factor or combination of growth factors, for example EGF, FGF, or EGF and FGF together, **into the ventricles** ..." Column 17, lines 8-12, emphasis added.

Weiss states:

> "The ventricular system is found in nearly all brain regions and thus allows easier access to the affected areas. If one wants to modify the stem cells in vivo by exposing them to a composition comprising a growth factor or a viral vector, it is relatively easy to implant a device that administers the composition **to the ventricle** and thus, to the neural stem cells. For example, a cannula attached to an osmotic pump may be used to deliver the composition. Alternatively, the composition may be injected directly **into the ventricles**." Column 26, lines 2-10, emphasis added.

Weiss states:

> "For treatment of Huntington's Disease, Alzheimer's Disease, Parkinson's Disease, and other neurological disorders affecting primarily the forebrain, growth factors or other neurological agents would be delivered **to the ventricles** of the forebrain ..." Column 26, lines 16-19, emphasis added.

In contrast, the instant invention provides a method for attracting a glial progenitor cell or a progeny thereof to a site of CNS lesion or damage, wherein TGF-α is administered **outside of the ventricles**, such that the glial progenitor cells present in the ventricles (e.g., the subependymal zone) proliferate and migrate away from the ventricles and toward a site of CNS damage or lesion.

Weiss does not show administration to a subject having CNS damage or lesion.

Weiss does not provide any disclosure showing administration of TGF-α to a subject having CNS damage or a CNS lesion, as required in the instant claims. **Where there is no lesion or CNS damage, there can be no migration to such.** Weiss only discusses experiments in which EGF, FGF, or a combination of EGF and FGF were introduced intraventricularly into mice that had **no CNS damage**

or CNS lesion. Weiss, Examples 27-30. Not one of the animals discussed in Examples 27-30 had CNS damage or lesion.

Weiss does not provide any teaching of administering TGF-α to stimulate migration of a glial progenitor cell or progeny thereof to a site of CNS damage or lesion. Weiss only discusses results of administering EGF, FGF, or a combination of EGF and FGF to ventricle of a mouse brain that does not have any CNS damage or lesion. Weiss only discusses proliferation of neural stem cells following intraventricular injection of EGF, FGF, or a combination of EGF and FGF. Weiss, Examples 27-30.

Weiss does not provide any evidence whatsoever that administration of TGF-α, with or without any other growth factors, will stimulate proliferation and migration of glial progenitor cells or progeny thereof to a site of CNS damage or lesion.

Weiss does not show any directed migration of neural progenitor cells or their progeny to a site of CNS damage or lesion.

Weiss does not show any directed migration of a glial progenitor cell or its progeny. Weiss does not show migration of a glial progenitor cell or its progeny away from the ventricle and toward a site of CNS damage or lesion. Weiss's experimental animals do not have any CNS damage or lesion. In the absence of a lesion, Weiss cannot teach or suggest that TGF-α would stimulate glial progenitor cell or its progeny to proliferate **and migrate toward a site of CNS damage or lesion**.

Weiss is not enabling for a method of attracting a glial progenitor cell to a site of CNS lesion or damage, involving administering TGF-α at or near a site of CNS lesion or damage, at a site outside of the ventricles.

It is well-settled law that a reference must be enabling in order to anticipate a claim. The Federal Circuit has stated in In re Donahue, 226 USPQ 619 (Fed. Cir. 1985) that:

> It is well settled that prior art under 35 U.S.C. § 102 (b) must sufficiently describe the claimed invention to have placed the public in possession of it. *In re Sasse*, 629 F.2d 675, 681, 207 U.S.P.Q. (BNA) 107, 111 (CCPA 1980); *In re Samour*, 571 F.2d at 562, 197 U.S.P.Q. at 4; see also *Reading & Bates Construction Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-52, 223 U.S.P.Q. (BNA) 1168, 1173 (Fed. Cir.1984). Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own

knowledge to make the claimed invention. See *In re LeGrice*, 301 F.2d at 939, 133 U.S.P.Q. at 373-74. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *In re Borst*, 52 C.C.P.A. 1398, 345 F.2d 851, 855, 145 U.S.P.Q. (BNA) 554, 557 (1965), cert. denied, 382 U.S. 973, 83 S. Ct. 537, 15 L. Ed. 2d 465 (1966).

Thus, if a reference is non-enabling for a particular invention, it cannot anticipate that particular invention.

As discussed above, Weiss does not show a method for attracting a glial progenitor cell to a site of CNS lesion or damage, involving administering TGF-α **to an individual having a CNS damage or lesion**, where administration is **outside of the ventricles**. Weiss does not show **migration** of a neural stem cell or progeny thereof away from the ventricles and to a site of CNS lesion or damage. Accordingly, Weiss is not an enabling disclosure, and as such cannot anticipate the instant invention as claimed.

Weiss does not disclose the instant method as claimed. Weiss is not an enabling disclosure. Accordingly, Weiss cannot anticipate the instant invention as claimed.

Applicants submit that the rejection of claims 1-8, 16, and 33 under 35 U.S.C. §102(e) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 1-7, 16, and 33 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Alexi et al. ((May, 1997) *Proc. Natl. Acad. Sci. USA* 77:5258-5262; "Alexi").

Alexi is not available as prior art under 35 U.S.C.§102(b). To be available as art under 35 U.S.C.§102(b), a reference must have been published more than one year before the effective filing date of the application. The instant application has an effective filing date of August 4, 1997. Alexi was published in May of 1997, i.e., less than one year before the effective filing date of the instant application. Accordingly, Alexi is not available as prior art under 35 U.S.C.§102(b). Alexi is available

as prior art under 35 U.S.C.§102(a).

Under 37 C.F.R.§1.131, and as discussed in MPEP §2132.01, when any claim of an application is rejected under 35 U.S.C.§102(a), the inventor of the subject matter of the rejected claim may submit a declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference on which the rejection is based.

The Declaration of James Fallon under 37 C.F.R.§1.131, provided herewith as Exhibit 3, states that the instant invention as claimed in rejected claims 1-7, 16, and 33 was conceived and reduced to practice before the May 1997 publication date of Alexi. The doctoral thesis of James Steven Reid (the "Reid thesis") provides evidence for the fact that the instant invention as claimed was conceived and reduced to practice before the May 1997 publication date of Alexi. The Reid thesis was deposited with the Office of Graduate Studies of the University of California at Irvine in March, 1997. A copy of the deposit form is provided herewith as Exhibit 5. The deposit form has been redacted to remove personal information.

As discussed above, the Reid thesis is not available as prior art to the instant application under 35 U.S.C.§102, as the Reid thesis was not publicly available until after the August 4, 1997 priority date of the instant application.

Applicants submit that the rejection of claims 1-7, 16, and 33 under 35 U.S.C. 102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Atty Dkt. No.: UCAL263CIP
USSN: 09/739,933

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL263CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Nov. 26, 2002

By: _____
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendments to claims 1, 20, and 33, as shown below.

1. (Amended) A method for attracting a glial progenitor cell, or a progeny of a glial progenitor cell, to a site of damage or lesion in a central nervous system (CNS) tissue, the method comprising [the steps of:]

[providing a compound that binds to an epidermal growth factor (EGF)/ ErbB family receptor; and]

administering a sufficient amount of [the compound] a compound that binds to an epidermal growth factor (EGF)/ ErbB family receptor, wherein said administration is outside of the ventricles, and wherein [to the site to attract] the glial progenitor cell or progeny thereof is attracted to the site of damage or lesion in the central nervous system (CNS) tissue.

20. (Amended) The method of claim 1, wherein the CNS tissue is in tissue culture, and wherein the compound is administered to [a] the tissue culture comprising a glial progenitor cell.

33. (Amended) A method for attracting a glial progenitor cell, or a progeny thereof, to a site of damage or lesion in a central nervous system (CNS) tissue, the method comprising administering a sufficient amount of transforming growth factor alpha (TGFα) polypeptide, or functional fragment thereof, to the site to attract the glial progenitor cell or its progeny to the site, wherein said administration is outside of the ventricles.